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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/627,757	07/28/2003	Yasuhiro Kouchi	Q76319	3310

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EXAMINER	
SITTON, JEHANNE SOUAYA	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 07/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/627,757	KOUCHI ET AL.	
	Examiner	Art Unit	
	Jehanne S. Sitton	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Currently, claims 1-5 are pending in the instant application. All the amendments and arguments have been thoroughly reviewed but are deemed insufficient to place this application in condition for allowance. The following rejections are newly applied as necessitated by amendment. They constitute the complete set being presently applied to the instant Application. Response to Applicant's arguments follow. This action is FINAL.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The previous rejections made under 35 USC 102 and 103 are moot in view of the amendments to the claims.

Claim Rejections - 35 USC § 112

4. Claims 1 and 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The amended claims are drawn to a method for predicting an increased risk for onset of open angle glaucoma based on the detection of at least one mutation in the coding region of the OPTN gene set forth in SEQ ID NO: 1, wherein the mutation is selected from: a) any mutation at

position 619 of SEQ ID NO: 1, and b) any mutation at position 898 of SEQ ID NO: 1, in any human subject, and predicting an increased risk for open angle glaucoma if at least one of said mutations is present. Dependent claims 4 and 5 also further limit claim 1 by reciting certain primer pairs for amplification of a polynucleotide sample.

All of the current claims encompass a large genus of nucleic acids which comprise any mutation or polymorphism at specific positions of SEQ ID NO: 1 which are not disclosed in the specification. The genus includes a large number of polymorphisms and mutations for which no written description is provided in the specification. This large genus is represented in the specification by only the particularly named 2 polymorphisms for which data is provided. This data, however, does not provide for a predictable association with any type of open angle glaucoma in any population, as is broadly claimed. Thus, applicant has express possession of only 2 particular polymorphisms in SEQ ID NO: 1, in a genus which comprises hundreds of different possibilities. Here, no common element or attributes of the sequences are disclosed which would permit selection of sequences as polymorphisms. No structural limitations or requirements which provide guidance on the identification of sequences which meet these functional limitations of associating a polymorphism with risk of glaucoma onset is provided. These claims expressly encompass all the different possible allelic variants including insertions, deletion, substitutions and transversions at the recited sites. However, no predictable correlation between the structural alterations of the 2 polymorphisms disclosed and a risk for glaucoma onset is provided by the specification. The specification does not teach the function of optineurin, nor how alterations are associated with glaucoma or an increased risk for glaucoma onset.

The specification provides no correlation between structure of polymorphisms and the function of such polymorphisms with an increased risk for open angle glaucoma onset. The polymorphisms shown are not representative of the genus of any mutation or polymorphism at the claimed sites which are associated with an increased risk for glaucoma onset because it is not clear which polymorphisms or mutations at those sites would have the same affect. The specification does not teach if the disclosed polymorphisms are disease affecting polymorphisms or whether they are linked to the causative mutations hundreds or thousands of nucleotides away. Accordingly, there is no description or guidance as to whether a C or T allele at the claimed sites even exist or would have the same affect, or whether any deletion, insertion or transversion exists or would have the same affect. The specification does not teach whether the polymorphisms shown affect the function of optineurin. The specification does not teach the function of optineurin nor how it's function, or lack of function, or altered function are predictably associated with glaucoma onset risk.

In analysis of the claims for compliance with the written description requirement of 35 U.S.C. 112, first paragraph, the written description guidelines note regarding genus/species situations that "Satisfactory disclosure of a ``representative number" depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of the species disclosed." (See: Federal Register: December 21, 1999 (Volume 64, Number 244), revised guidelines for written description.) In the instant case, the specification fails to teach the necessary common attributes or features of the genus of encompassed nucleic acids and polymorphisms in view of the species disclosed. As such, one of skill in the art would not

recognize that applicant was in possession of the genus of nucleic acids and polymorphisms encompassed by the broadly claimed invention.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116.)

The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acids and polymorphisms, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993), and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. The current situation is a definition of the compound solely based on its functional utility, as a polymorphism, without any definition of the particular polymorphisms claimed.

Finally, University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that:

To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (" [T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d at 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

Response to Arguments

5. The response asserts that the claims have been amended to recite a method limited in scope to one disease, one patient population, one gene, and at least one of two mutations. This argument has been thoroughly reviewed but was not found persuasive for the reasons set forth above.

6. Claims 1-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is undue. These factors have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention and the breadth of the claims:

The amended claims are drawn to a method for predicting an increased risk for onset of any type of open angle glaucoma based on the detection of at least one mutation in the coding region of the OPTN gene set forth in SEQ ID NO: 1, wherein the mutation is selected from: a) any mutation at position 619 of SEQ ID NO: 1, and b) any mutation at position 898 of SEQ ID NO: 1; in any human subject, and predicting an increased risk for any type of open angle glaucoma if at least one of said mutations is present. Dependent claims 4 and 5 also further limit claim 1 by reciting certain primer pairs for amplification of a polynucleotide sample. Dependent claims 2 and 3 limit claim 1 to an A to G substitution at position 619, or G to A at position 898 in SEQ ID NO: 1 (claims 2 and 3, respectively).

The nature of the claimed invention, therefore requires the knowledge of predictable associations between the presence of any mutation at the indicated sites in SEQ ID NO: 1 and increased risk of onset of any type of open angle glaucoma in any human subject.

The amount of direction or guidance and Presence and absence of working examples:

The specification teaches that blood from patients diagnosed as having open angle glaucoma were used to determine the sequence of the OPTN gene and compared to a non patient group (page 18). The specification teaches at page 15, that SEQ ID NOS: 21 and 22 were used to amplify exon 7 and SEQ ID NO: 27 and 28 were used to amplify exon 10. The specification teaches the identification of two mutations: A to G at position 619 and G to A at position 898 relative to SEQ ID NO: 1. The specification teaches that the frequency of the polymorphism at position 619 was 1.4 % in the patient group, and 0% in the non patient group, while the

frequency of the polymorphism at position 898 was 0.8% in the patient group and 0% in the non patient group (page 19).

However, the specification is silent as to whether the frequency of the disclosed polymorphisms was statistically significant, as to how many patients and controls were tested, as to what the population origin of the patients and controls were (Caucasian, African, Japanese, Chinese, etc) and as to what type of open angle glaucoma the patients suffered from (primary adult onset: POAG or juvenile JOAG).

Further, the specification does not teach the function of the OPTN gene, or how the mutations detected affect the function of the OPTN gene, such that one of skill in the art could establish that a predictable correlation exists between the presence of any mutation in the recited position and any type of open angle glaucoma in any human subject.

In light of the unpredictability taught in the art with regard to these factors, the specification does not enable one of skill in art to practice the method as broadly as it is claimed, without undue experimentation.

The state of the prior art and the predictability or unpredictability of the art:

At the time the invention was filed, the function of ~~the~~ optineurin was not known, and the art provided no predictable structure function correlation between any mutations in the coding region of OPTN and risk of onset of glaucoma. Rezaie (Rezaie et al; Science, vol. 295, pages 1077-1079, 2/2002) teaches that the function of OPTN is unknown. While Vittitow (Vittitow et al; Biochemical and Biophysical Research Communications, vol. 298, pages 67-74, 2002) teaches that expression of optineurin is increased in response to increased intraocular pressure

(abstract), Kamphius (Kamphius et al; Ophthalmic Research, vol. 35, pages 93-96, 2003) teaches that optineurin gene expression level in the human trabecular meshwork was not changed in response to pressure elevation (see abstract).

The claims have been amended to recite any type of open angle glaucoma, however, the post filing date art demonstrates the unpredictability of associating mutations in OPTN, with any type of glaucoma in different patient and non patient populations.

While Rezaie teaches that the R545Q mutation appears to be a disease causing mutation in Caucasian patients with adult onset POAG, Alward (Alward et al; Am. J. Ophthalmology, vol. 136, pages 904-910, 2003) teaches that it is likely to be a non disease causing polymorphism with marked ethnic differences in prevalence (see para bridging cols 1 and 2, page 109). Further, while Rezaie teaches that the M98K mutation appeared to be a risk associated alteration for NTG (table 1), Alward teaches that the M98K mutation was associated with a fraction of NTG only in patients with Japanese ethnicity but not in Caucasians (see abstract, col. 2, page 909). Further, Willoughby (Willoughby et al; IOVS, 2004; vol. 45, pages 3122-3130) teaches that the OPTN M98K change, which had been reported as a susceptibility allele for POAG, was studied and "may confer a susceptibility risk to POAG, but does not appear to predispose to JOAG" (see page 3128, col. 1, 2nd full para). Leung (Leung et al; IOVS, September 2003, vol 44, pages 3880-3884), on the other hand, teaches that M98K and R545Q appear to be common polymorphisms in the normal Chinese population (page 3882, col 2). Alternatively, Tang (Tang et al; Human Genetics, vol. 113, pages 276-279; 2003) teaches that none of previously reported NTG risk mutations showed any significant differences among Japanese (see page 278, col. 1, "Discussion"). Further, Tang teaches that 10 out of 392 normal chromosomes contained the G to

A mutation at position 1944 in the Japanese population, which differed from the 0 out of 100 chromosomes reported by Rezaie for Caucasians. Tang further exemplifies the need to provide large sample sizes for analysis. Wiggs (Wiggs et al; Arch. Ophthalmology. Vol. 121, 2003, pages 1181-1183) teaches analysis of mutations in exons 4 and 5, reported to be recurrent mutations in patients with NTG, in patients with adult onset POAG, and teaches that these mutations do not appear to be associated with adult onset POAG (see abstract).

The detection of new polymorphisms is an entirely unpredictable art which is empirical in nature, and once these polymorphisms are detected, their association with a phenotype, in this case, different types of open angle glaucoma, must be established before they can be used in a predictive manner. Even if an association is demonstrated between a single polymorphism within a gene and a phenotype, it is not necessarily a predictor that a different polymorphism or mutation at that position within the gene will also have the same predictive ability. The specification does not teach if the disclosed polymorphisms are disease affecting polymorphisms or whether they are linked to the causative mutations hundreds or thousands of nucleotides away. Accordingly, there is no guidance as to whether a C or T allele at the claimed sites even exist or would have the same affect, or whether any deletion, insertion or transversion exists or would have the same affect.

The level of skill in the art:

The level of skill in the art is deemed to be high.

The quantity of experimentation necessary:

In order to practice the invention as claimed, one would first have to establish that a predictive relationship exists between the disclosed polymorphisms and any type of open angle glaucoma in any patient population. Given the lack of any information regarding sample size, patient and non patient populations, and statistical significance of the observed frequencies, such experimentation would be unpredictable as it cannot be established whether the observed frequencies were due to chance or would only be observed in such frequencies in a specific population, ie: Caucasian vs Chinese. The investigations set forth to support the instantly claimed invention are not independently replicated. In a technology that is known to be highly unpredictable, made more so by the lack of any structure function correlation between the disclosed polymorphisms and glaucoma, the lack of guidance with regard to sample size and population analysis is a particular cause for concern. Further, the specification does not teach whether the polymorphisms shown affect the function of optineurin nor how it's function, or lack of function, or altered function are predictably associated with glaucoma onset risk.
Further, the scope of claims 1 and 4-5 requires knowledge of an association between all mutations in the recited positions of SEQ ID NO: 1 and any type of open angle glaucoma in any human population, which as exemplified by the teachings in the art, is highly unpredictable. Although claims 2 and 3 recite specific polymorphisms, they are broadly drawn to risk to any type of open angle glaucoma as well as any human population. Due to the scope of the claims, one would be required to further undertake extensive trial and error experimentation with a large number of patients with different types of glaucoma, and controls, including in different racial populations, to determine mutations that share a predictive increased risk of glaucoma onset.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification, the high level of unpredictability in the associated technology, the nature of the invention, and the quantity of unpredictable experimentation necessary to practice the claimed invention, it would require undue experimentation to practice the invention as claimed.

Response to Arguments

7. The response asserts that the claims have been amended to recite a method of predicting the onset of a specific disease, in a specific patient population by screening for at least one of two specific mutations in one specific gene. This argument has been thoroughly reviewed but was not found persuasive. Although the claims have been amended to recite "open angle glaucoma", which was not previously claimed, the recitation does not set forth a specific disease but rather includes different diseases with different phenotypes and risk associations. Additionally, the claims are not limited to a specific patient population, as the broadly encompass any human subject. However, mutations in optineurin have been found to be differently diagnostic depending on different ethnic/racial populations. However, the specification provides no teaching of the predictability of associating the disclosed polymorphisms in different populations, which the art exemplifies is an unpredictable undertaking. Additionally, claims 1, 4, and 5 are not limited to the specific polymorphisms at positions 619 or 898, but rather encompass a large number of different possible mutations at such positions. However, the specification provides no guidance as to what mutations at such position would predict an increased risk for onset of any type of open angle glaucoma. The specification does not teach whether the polymorphisms shown affect the function of optineurin nor how it's

function, or lack of function, or altered function are predictably associated with glaucoma onset risk. The specification does not teach if the disclosed polymorphisms are disease affecting polymorphisms or whether they are linked to the causative mutations hundreds or thousands of nucleotides away. Accordingly, there is no guidance as to whether a C or T allele at the claimed sites even exist or would have the same affect, or whether any deletion, insertion or transversion exists or would have the same affect. The response refers to a declaration submitted under 37 CFR 1.132 by Yasuhiro Kouchi as providing further evidence of the patient population. The declaration has been thoroughly reviewed but was not found persuasive to overcome the rejection. The declaration sets forth that for the polymorphism at position 619: there were 70 subjects in the patient group, only 1 of which was shown to have the mutation, and 120 subjects in the non patient group, none of which had the mutation. The declaration sets froth that for the polymorphism at position 898: there were 128 subjects, only 1 of which had the polymorphism, and 80 control subjects, non of which had the polymorphism. However, a single occurrence of an alternate allele in a specific population does not provide a predictable correlation that such polymorphism is actually associated, either by affecting the function of the gene or encoded protein, or by linkage in a specific disease associated haplotype to a causative mutation, with a disease. It cannot be determined whether the occurrence of such mutation is due to chance or is actually disease associated. The function of optineurin is not taught, therefore the effect of the polymorphisms on the function of optineurin are unknown. Further, it is not known whether the polymorphisms are linked to a disease associated haplotype. The specification does not make up for the art accepted unpredictability of associating particular mutations in any type of glaucoma, let alone any type of open angle glaucoma, in "any" human population, as is broadly claimed.

The conflicting teachings of the art cited above, specifically exemplifies that even particular mutations which altered the amino acid sequence of optineurin and were found in multiple patients are unpredictably disease associated in different populations and different type of glaucoma. Here, the case is that a single alternative allele has been found. However, the study has not been independently replicated in different populations, nor has any assessment been made as to whether the presence of the alternative allele is due to chance, or is actually disease associated. The declaration does not make up for the deficiencies in the specification, which are critical to enabling the methods of the claimed invention, as shown by the unpredictability in the art cited above.

8. Claims 1-5 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 sets forth the recitation "the optineurin gene set forth in SEQ ID NO: 1". However, SEQ ID NO: 1 is not the sequence of the optineurin "gene". Accordingly, the claims reliance on the term 'gene' is unclear.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

10. No claims are allowed.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jehanne Sitton whose telephone number is (571) 272-0752. The examiner can normally be reached Monday-Thursday from 8:00 AM to 5:00 PM and on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, can be reached on (571) 272-0735. The fax phone number for this Group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Jehanne Sitton
Primary Examiner
Art Unit 1634
7/14/06